

## Translation of Examples and Claims from WO 02/34713

(54) Title: Process For Producing B-Form Nateglinide Crystals

(Patent p.3)

### Implementation Example 1

Nateglinide H-form crystals (24.5 kg) were added to ethanol (360 L) and stirred to dissolution at room temperature. After dissolution was confirmed (the mixture) was cooled to 5°C and allowed to mature at 5°C for one hour. The deposited crystals were separated and damp crystals (43.0 kg) obtained. These were dried at 45°C in a rack drier for 24 hours (water content ca. 1%) and then heated for 12 hours at 90°C to bring about a crystal transformation, when dry crystals (13.3 kg) were obtained. When these crystals were measured by DSC, the characteristic B-form peak was detected (mp ca. 130°C) but the characteristic H-form peak (mp ca. 139°C) was not detected. Hence the crystals obtained were of the B-form only and the H-form was concluded to be essentially absent.

(Patent p. 6)

### Scope Of Patent Claims

1. A method for producing nateglinide B-form crystals essentially free of the H-form which consists of drying the damp solvate crystals of nateglinide at low temperature until the solvent has disappeared and subsequently inducing a crystal transition.
2. A method for producing nateglinide B-form crystals according to Claim 1 above, where, in the B-form crystals obtained there is no detectable H-form when measured by DSC.
3. A method for producing nateglinide B-form crystals according to Claim 1 above where the drying takes place at below 50°C.
4. A method for producing nateglinide B-form crystals according to Claim 1 above where the drying is carried out until the solvent essentially disappears.
5. A method for producing nateglinide B-form crystals according to Claim 1 above where the above mentioned solvate is the hydrate.
6. A method for producing nateglinide B-form crystals according to Claim 1 above where the crystal transformation is carried out by heating at 60 to 110°C.
7. A method for producing nateglinide B-form crystals according to Claim 1 above where both the processes of low temperature drying of the moist nateglinide crystals, and the crystal transformation are processes which can be carried out on an industrial scale.
8. A method for producing nateglinide B-form crystals containing essentially no H-form crystals, which comprises the following: the solvate crystals consisting of nateglinide hydrate, as separated on crystallization by cooling from a solution of nateglinide, are dried below a temperature of 50°C until the solvent has disappeared and the solvate essentially no longer exists, after which, by heating at 60 to 110°C a crystal transformation to the B-form is brought about.
9. A method for producing nateglinide B-form crystals according to Claim 8 above where the nateglinide B-form crystals, when measured by DSC, are crystals in which the H-form cannot be detected.

Translation of Sections on Heating from WO 02/34713

(Patent p.3, line 2)

The moist solvate crystals obtained (BS: from the cooled solution) are dried till the solvent disappears. The temperature for this will differ depending on the type and quantity of solvent, but usually lies below 60°C and preferably below 50°C. Although there is no lower limit to the temperature, it (the drying) is usually carried out at 20°C or more for economic reasons. Drying is favourably carried out at usual reduced pressure; at industrially attainable reduced pressures the drying will be complete in a short time.

Though the drying at low temperature can be continued to virtual disappearance of the solvent it is not necessary to clear it completely. Even if solvent to the extent of 5% by weight is present this is no problem because it will disappear during the crystal transformation.

By heating the dried crystals at 60 - 110°C, preferably 70 - 100°C, a crystal transformation into the B-form is brought about. Though the crystal transformation is usually favourably carried out in 0.5 to 48 hours, a period of 1 - 24 hours is most favoured.